Regression standardization and attributable fraction estimation with between-within frailty models for clustered survival data

Abstract: In epidemiological studies the relationship between an exposure and the time to some outcome is usually presented as a hazard ratio. However, the hazard ratio is a relative measure that does not give any information about the impact of the exposure on the time to the outcome on a population level. In public health and policy making interest is usually in how the prevalence of some disease can be reduced by some intervention targeted at reducing an exposure that we expect to cause the disease. The attributable fraction (or attributable risk) and standardization are useful measures in public health since it inform about the population impact of an exposure on an outcome. In this study we analyze the relationship between preterm birth (born before week 37 of gestation) and the time-to ADHD diagnosis. We expect that the relationship between preterm birth and ADHD is confounded by unobserved familial factors such as genes and childhood environment. In the presence of unobserved confounding we cannot estimate the causal effect of preterm birth on ADHD. A solution is to use family data and compare siblings born by the same parents but with discordant status in preterm birth. The main method that is used to adjust for family shared confounders in survival data is the stratified Cox model. However, the stratified Cox model cannot estimate absolute effects and thus, we cannot use the model to estimate standardized survival curves or the attributable fraction function. An alternative method is the frailty model (which parallels the random effect model for point outcomes). The limitation with the ordinary frailty model is that it does not adjust for family shared unobserved confounding. However, the between-within model adjust for family shared unobserved confounding and can be used for standardization. In this work we present how the between-within model can be used for standardization and the estimation of the attributable fraction. As an illustration of the difference between the stratified Cox model, the frailty model and the BW model we use data from Swedish registries in a within-mother-between-pregnancy analysis of preterm birth on the time-to ADHD diagnosis/medication. We also estimate standardized survival curves and the attributable fraction function for preterm birth and ADHD.

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